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EXAMINER
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1655	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/306,333	Applicant Jan Vijg
	Examiner Jehanne Souaya	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 26, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4-11* is/are pending in the application.

4a) Of the above, claim(s) *7-9* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4-6, 10, and 11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Currently, claims 4-11 are pending in the instant application. Claims 7-9 have been withdrawn from consideration as being drawn to non-elected subject matter (see restriction requirement below). The amendments and arguments have been thoroughly reviewed but were not found sufficient to place the instant application in condition for allowance. Finality of the previous office action has been withdrawn. A new office action follows. This action has been made final as it addresses issues raised due to applicant's amendment and response filed Oct 25, 2000. Response to Applicants arguments follow.

2. It is noted that the after final response mailed Sept 26 2001 has not been entered, therefore, SEQ ID NOS 121 and 122 have not been deleted from the substitute specification. It is further noted that the response after final rejection, received October 26, 2001, which has been entered, does not delete these sequences. In the office action mailed 7/31/01, the examiner raised the issue of new matter regarding these sequences as they were not present in the specification as originally filed. This matter must be addressed in applicant's response to the following office action as the amendment filed October 25, 2000 is still objected to under 35 U.S.C. 132 because it introduces new matter (Seq ID NO: 121 & 122) into the disclosure.

gp 12/12/01

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 4-6 and 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-6 and 10-11 are indefinite as it cannot be determined which primers with SEQ ID NOS 37-46 are paired with a particular exon fragment.

The claims are further indefinite as it cannot be determined which primers 47-120 are used with a particular exon fragment to produce second set of amplification products.

The claims are further indefinite as it is unclear which clamping sequence is paired with a particular primer or exon. The claims simply group these primers and clamping sequences together, without making clear the relationship between a particular exon, primer, primer pair, or clamping sequence.

The claims are further indefinite as it cannot be determined whether the clamping sequences are attached to primers or to exons.

Claim 10 is indefinite as the term "said short distance PCR" lacks proper antecedent basis. The term from which it depends recites "short distance *multiplex* PCR". Appropriate correction is required.

Specification

6. The amendment filed October 25, 2000 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Newly added table 4 recites SEQ ID NOS not identified in the original specification. The original specification listed a clamp name next to a specific primer sequence (see p. 10 of specification as originally filed), however neither a SEQ ID NO nor an actual sequence was taught or defined corresponding to a clamp name. One of ordinary skill in the art would not have been able to deduce the specific nucleic acid sequence of these clamps (GC 3, GC 13, GC 12, etc) given the disclosure in the specification as originally filed, or from the prior art. Neither the specification, nor the prior art define which sequence corresponds to which clamp nor which primer or exon sequence it was paired with. Consequently, the pairing of SEQ ID NOS 27, 29-32 with an exon or primer from table 4 constitutes new matter. It is noted that the instant claims are drawn to this new matter.

Applicant is required to cancel the new matter in the reply to this Office action.

New Grounds of Rejection

The following rejection is newly applied as it cites additional grounds for rejection not made in the previous office action. However, as the *originally* filed claims were not directed to the limitation of using clamping sequences, this rejection addresses claim limitations introduced

after the first office action (had these claim limitations been introduced in the amendment following the first office action, this rejection would have been applied in a final office action, consequently, the present office action is made Final).

7. Claims 4-6 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vijg, Jan (WO 96/39535 referred to as VIjg) in view of Vijg et al (Vijg II, US Patent 6,007,231), Park et al (US Patent 5,948,697) and Liskay et al (US Patent 5,922,855) .

Vijg teaches a method for diagnostic testing of DNA using PCR amplification followed by electrophoretic separation of the resulting fragments to detect possible gene variants of mutational defects (see abstract), specifically in the retinoblastoma gene. Vijg teaches that with the method, it is possible to test individual at any time for inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases (see p. 3, lines 1-8). The method taught by Vijg comprises amplifying regions of target DNA, usually protein coding regions (exons), by PCR (see p. 6, lines 20-23) using primers which have been positioned to cover the exons. Vijg teaches that these amplification reactions are conducted separately, eg., if 27 exons in a gene are being analyzed, then 27 separate PCR reactions must be conducted, but also teaches that it is usually possible to conduct a few PCR reactions together in one tube (see p. 7, first para). Vijg then teaches that primers for short PCR are positioned such that a) the desired target sequences should be covered by amplicons of between 100 and 600 bp, b) amplicons should have optimal melting behavior, ie: consist of one lowest melting domain in addition to the GC-clamp attached to one of the primers, c) optimal amplicon distribution over a

2D gel, and d) similar reaction kinetics (See table 1, p. 13). Vijg then teaches that the PCR conditions are set up separately for each primer set with the long-PCR products as template for the short PCR and that multiplex co-amplification conditions are developed by grouping primer sets and adjusting reaction components. After the PCR, Vijg teaches that the mixture of fragments are subjected to 2-D electrophoresis in a denaturing gradient gel(see p. 16, lines 16-20).

Although Vijg does not teach testing gene sequences of the BRCAI gene, Vijg does teach the use of the method to generally detect sequence mutations in any gene, provided the nucleotide sequence of the gene is known, and specifically teaches analyzing the retinoblastoma gene. The BRCAI gene sequence was well known in the art at the time of the invention, as was the link between mutations in this gene in different types of cancer (BRCAI in breast and ovarian cancer). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Vijg to detect mutations in the BRCAI gene as Vijg teaches the usefulness of the method in detecting inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases. The ordinary artisan would have been motivated to use the method taught by Vijg to detect mutations in BRCAI as both Liskay et al and Park et al teach mutations in the BRCAI gene and its link to cancer. The ordinary artisan would have had a reasonable expectation of success that using the method taught by Vijg, primers could be generated that would successfully amplify the necessary coding regions of both the BRCAI gene and provide characteristic 2-D spot patterns for certain

mutations as Vijg and Vijg II both teach in extensive detail (see pp 7-10, 18-19 of Vijg; and col.2, col.6, col.9, and claim 1 of Vijg II) how to prepare primers that would be successful in the method taught by Vijg given a known gene sequence.

With regard to the claim limitation drawn to "include two clamping sequences for each..." it is noted that Vijg II teaches (claim 2) a method in which, in the event of overlap clustering of PCR fragments along the one dimension, changing the position of primers and/or changing the size of the GC clamp sequences. Vijg II further teaches (claim 5) a method in which varying of the length of the GC clamp letter sequence is effected by adding a second GC clamp sequence. Thus Vijg II expressly teaches using two clamping sequences in the event of overlap clustering of PCR fragments. It is further noted that Vijg teaches that GC clamps are essential to guarantee the highest sensitivity to detect mutations in the denaturing gradient gel. Thus, it was known in the art at the time of the invention that a using a GC clamp was important for highest sensitivity. It would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to provide a second GC clamp for the purposes of increasing sensitivity as it was known in the art that a GC clamp improved sensitivity of denaturing gradient gels. The courts have held that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069,

1072 (CCPA 1980) [see MPEP 2144.06]. See further *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) [MPEP 2144.06 VI.B] regarding duplication of parts.

Response to Arguments

All previously entered amendments, arguments and the declaration have been thoroughly reviewed but were found unpersuasive to place the instant application in condition for allowance.

In the office action 5/16/00, the examiner indicated to applicants that a showing of unexpected results could aid applicant in overcoming the rejection made under 35 103(a). In response, applicant filed a declaration stating that it was necessary to require the splitting of the BRCA1 gene into fragments. The examiner responded " With regard to the need to split the BRCA1 gene into fragments, the ordinary artisan would have been motivated to do so as the BRCA1 gene is larger than the RB1 gene, and as the detection method of Vijg involves electrophoresis, the ordinary artisan would have known that smaller amplification products would have improved clarity and resolution in gel electrophoresis." It is further noted that Vijg teaches that the desired target sequences should be covered by amplicons of between 100 and 600 bp.

The declaration further stated that "clamps of variable sequence and links were found to be necessary to induce a stable melting domain, specifically the pairs of clamping units shown for exons 11.1... etc in Table 4". Further, the declaration points to Figs 1A and 1B as a showing of rather remarkable resolution. Firstly, it is noted that the clamping sequences of table 4 are directed to new matter. Secondly, with regard to using clamps of variable sequence, both Vijg

and Vijg II teach using clamps of varying sequence (See Vijg II, claim 2; and Vijg: Table 2- GCI, GCII, and GCIII correspond to a 30mer, 38mer, and 35mer respectively). In the office action mailed 7/31/01, the examiner erroneously indicated that the use of clamping and linking sequences constituted unexpected results, given the disclosure in the declaration. A thorough search of the prior art, however, indicated that the concept of using clamping sequences of varying length were known and used at the time of the invention, and were disclosed in applicants own prior art references. (See rejection made above). As a result of such erroneous indication, the finality of the previous office action has been withdrawn, and a new final rejection, addressing issues brought about by amendment of the specification and claims after the first office action, has been issued to clarify the written record.

With regard to the showing of unexpected and improved resolution shown in Photos 1B and 1A, it is noted that no basis for comparison has been set forth illustrating the improved and "rather" remarkable clarity, resolution and reliability of these photos. Firstly, the copy of these figures in the specification are unclear, especially the photographs. Secondly, the specification provides no basis that these photos represent unexpected and improved resolution, such that no comparison can be made to assess these unexpected and improved results. With regard to the use of two clamping sequences, applicants have not provided a reason as to why the use of two clamping sequences would not have been expected, to one of ordinary skill in the art, to give increased sensitivity and resolution, given the disclosure in the prior art with regard to the claims

of Vijg II, the teaching of Vijg that GC clamps are required for highest sensitivity, and case law addressing combining or duplicating parts known to have a specific effect.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1655
12/12/01

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600